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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/618,443
Filing Date: July 11, 2003
Appellant(s): LINDER ET AL.

Theodore Allen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 9, 2007 appealing from the Office action mailed October 13, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,969,585	**Lorincz et al.**	**29-November 2005**
6,165,723	**Shah et al.**	**26-December 2000**
WO93/10263	**Challberg et al.**	**27-May 1993**
6,280,946	**Hyldig-Nielsen et al.**	**28-August 2001**

Kumar et al. (Bioorganic & Medicinal Chemistry, 1998, vol. 8, p. 2219-2222)

Bruchez, Jr. et al. (Science, 1998, vol. 281, p. 2013-2016)

5,256,535 Ylikoski et al. 26-October 1993

Fukasawa et al. (Science, 1996, vol. 271, p. 1744-1747)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claim 28 is rejected under 35 U.S.C. 102(e) as being anticipated by Lorincz et al. (US Patent 6,969,585; November 2005). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

With regard to claim 28, Lorincz teach a method for identifying a sensor which specifically binds to a desired target, comprising:

a) contacting a sample suspected of containing a target of interest with a detectable sensor, wherein said contacting takes place in a preservative solution comprising an amount of one or more water soluble alcohols effective to preserve such solution against at least one contaminant (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection; col. 10, where the formulation of the universal collection medium are listed, which comprise an alcoholic preservative solution; see Examples 3-5, where samples were incubated and hybridized in UCM formulations indicated at col. 10); and

b) detecting whether said sensor has bound to said target (Example 1, col. 10, lines 1-5, where the plate was read in a luminometer and data was expressed as signal-to-noise).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-4, 8-12, 14-16, 18-19 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz et al. (US Patent 6,969,585; November 2005) as applies to claim 28 above and further in view of Shah et al. (US Patent 6,165,723; December 2000). Lorincz teaches

a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

With regard to claim 1, Lorincz teach a method comprising:

a) providing a sample that is suspected of containing a target (example 1, col. 10, where the protocol of detecting a nucleic acid is taught; example 3-5, the samples were HPV 16 positive cancer cells, CaSki were placed in the universal collection medium and tested for HPV DNA or RNA targets);

b) providing a sensor that can bind to the target in an alcoholic preservative solution, said sensor conjugated to a chromophore (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection; col. 10, where the formulation of the universal collection medium are listed, which comprise an alcoholic preservative solution; see Examples 3-5, where samples were incubated and hybridized in UCM formulations indicated at col. 10);

c) contacting the sample with the sensor in the alcoholic preservative solution under conditions in which the sensor can bind to the target, if present (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection); and

e) detecting the target (Example 1, col. 10, lines 1-5, where the plate was read in a luminometer and data was expressed as signal-to-noise).

With regard to claim 2, Lorincz teach an embodiment of claim 1, wherein the sample is selected from the group consisting of a urine, a vaginal swab, a pap smear, a needle biopsy and a section of tissue (col. 7, lines 46-57, where multiple methods of obtaining cells are noted, including those listed).

With regard to claims 3 and 4, Lorincz teach an embodiment of claim 1, wherein the sensor comprises an aptamer and a polynucleotide (col. 2, lines 59-61, where DNA, RNA, protein or carbohydrates are measured; col. 9, lines 32-39).

With regard to claim 14, Lorincz teach an embodiment of claim 1, wherein the target is DNA (col. 2, lines 59-61, where DNA, RNA, protein or carbohydrates are measured; col. 9, lines 32-39).

With regard to claim 15, Lorincz teach an embodiment of claim 1, wherein the target is RNA (col. 2, lines 59-61, where DNA, RNA, protein or carbohydrates are measured; col. 9, lines 32-39).

With regard to claim 16, Lorincz teach an embodiment of claim 1, wherein the sample is a cellular fraction (Example 3-5, where HPV 16 positive cancer cells (CaSki) were placed in UCM and other fixatives and where the cells were studied at a concentration of $0.8x\ 10^6$ cells).

With regard to claim 18, Lorincz teach an embodiment of claim 1, wherein said target is a pathological organism or component or product thereof (Examples 3-5, where the target is HPV).

With regard to claim 19, Lorincz teach an embodiment of claim 1, wherein the target is a virus or component or product thereof (Examples 3-5, where the target is HPV).

With regard to claim 23, Lorincz teach an embodiment of claim 1, further comprising washing said sample prior to said detecting (Example 1, col. 10, lines 64-66, where wells were washed 6x after hybridization and prior to detection).

With regard to claim 24 and 25, Lorincz teach an embodiment of claim 1, wherein the sensor is conjugated to a detectable moiety and where the sensor is itself detectable (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection).

With regard to claim 26, Lorincz teach an embodiment of claim 1, wherein the method is automated (col. 9, lines 46-67, where the method can be carried out using devices adapted to the method).

With regard to claim 27, Lorincz teach an embodiment of claim 1, wherein the method is performed manually (col. 9, lines 46-67, where in the converse situation, the method can be carried out without using devices adapted to the method).

Regarding claim 1, Lorincz teaches the method of binding a sensor to a target in an alcohol containing solution, however Lorincz does not teach the steps directed to d) applying a light source to the solution that can excite the chromophore and e) detecting whether light is emitted from the target.

With regard to claim 8, Shah teach an embodiment of claim 1, wherein the chromophore is a fluorophore (col. 9, lines 5-30, where a fluorescein labeled probe complementary to B. microti was hybridized to fixed cells).

With regard to claims 9 and 11, Shah teach an embodiment of claims 8 and 9, wherein the fluorophore is a fluorescent dye (col. 9, lines 5-30, where a fluorescein labeled probe complementary to B. microti was hybridized to fixed cells).

With regard to claim 12, Shah teach an embodiment of claim 11, wherein the fluorescent dye is fluorescein (col. 9, lines 5-30, where a fluorescein labeled probe complementary to B. microti was hybridized to fixed cells).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the probe taught by Lorincz to substitute a direct chromophore label as taught by Shah for the biotin label currently disclosed. As noted by Shah, "The sample is then rinsed with Evans Blue to counter stain the host cell, so as to see clearly fluorescent labeled probe(s) bound to specific nucleic acids of the pathogens which may be present within the sample (e.g., within the cells of the sample)" (col. 2, lines 59-63). Furthermore, as noted by Shah, "This procedure allows for the use of non-radiolabeled probes, which have a much longer shelf life and do not require special storage space. Either direct detection system using dark field microscopy can be used" (col. 6, lines 1-4). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the direct fluorescent label taught by Shah for the biotin label taught by Lorincz with a reasonable expectation for success.

3. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of

Challberg et al. (WO93/10263; May 1993). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above.

However, Lorincz does not explicitly teach the inclusion of control samples in the practice of the method exemplified at Examples 1-3. Challberg teaches a technique for the detection of genetic defects, microbial infections or viral infections (Abstract).

With regard to claim 20, Challberg teach an embodiment of claim 1, further comprising comparing a result from said detecting to a result obtained from a control sample (Example 4, where samples were tested by pipetting hydrolysis reagent into control and sample tubes; Table IV).

With regard to claim 21, Challberg teach an embodiment of claim 20, where the control sample is a positive control (p. 26, lines 8-13, where a kit for practice of the disclosed method should contain a positive control, preferably 150 pm biotinylated PCR product).

With regard to claim 22, Challberg teach an embodiment of claim 20, where the control sample is a negative control (p. 26, lines 8-13, where a kit for practice of the disclosed method should contain a negative control, preferably a mock PCR reaction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Lorincz to incorporate the sample controls taught by Challberg to arrive at the claimed invention with a reasonable expectation for success. As taught by Challberg, "The kit should contain a negative control and a positive control for

each probe. Preferably, the negative control is mock PCR reaction buffer. The positive control preferably contains 150 pM 5'-biotinylated PCR product in a mock PCR reaction" (p. 26, lines 8-13). Furthermore, the inclusion of both a positive and a negative control for each individual probe in the assay ensures reproducibility and reliability of each replicate of the assay. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the control samples taught by Challberg to the method of target detection taught by Lorincz to achieve reliable and sensitive detection of target sequences, and HPV infection, specifically.

4. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) as applied to claim 28 above, and further in view of Challberg et al. (WO93/10263; May 1993). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz teaches all of the limitations of claim 28 as recited in the 102 rejection stated above. However, Lorincz doesn't teach the application of the method of claim 1 to a plurality of candidate sensors. Challberg teaches a technique for the detection of genetic defects, microbial infections or viral infections (Abstract).

With regard to claim 29, Challberg teaches an embodiment of claim 28, wherein the method is performed on a plurality of candidate sensors (p. 26, Example 1, where Probes A, B and C were incorporated into the method of detection and wherein each of these probes were specific for a plurality of types of HPV virus).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Lorincz to incorporate the plurality of candidate sensors taught by Challberg to arrive at the claimed invention with a reasonable expectation for success. As taught by Challberg, "Numerous types of HPV have been identified, and not all HPV infections are oncogenic. For example, HPV 6 and HPV 11 are associated with benign lesions, whereas HPV 16 and HPV 18 are detected in cervical and other anogenital cancers and their precursor lesions. The determination of the type of HPV infection is therefore essential for proper diagnosis, risk assessment of cancer development and treatment". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the plurality of candidate sensors taught by Challberg into the method of detection taught by Lorincz to achieve proper determination of the specific viral types present in the sample(s) being tested.

5. Claim 5, 7, 29 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Hyldig-Nielsen et al. (US Patent 6,280,946; August 2001). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion

of a probe which comprises peptide nucleic acid (PNA) or the inclusion of a plurality of probes each of which comprises a corresponding detectable label.

Hyldig-Nielsen teaches the inclusion of a peptide nucleic acid probe into a method of multiplex-FISH analysis (Abstract).

With regard to claim 5, Hyldig-Nielsen teach an embodiment of claim 1, wherein the sensor comprises a peptide nucleic acid (Abstract, col. 10, lines 58-66, where PNA probes represent a preferred embodiment of the invention).

With regard to claim 7, Hyldig-Nielsen teach an embodiment of claim 1, wherein the sample is contacted with a plurality of different sensors, each of said plurality comprising a corresponding detectable label, wherein each of said plurality can selectively bind to a corresponding different target (col. 7, lines 58-63, where the invention is directed towards multiplex analysis; col. 15, lines 60-63, where each individual probe is independently detectable).

With regard to claim 29, Hyldig-Nielsen teach an embodiment of claim 28, wherein the method is performed on a plurality of candidate sensors (col. 7, lines 58-63, where the invention is directed towards multiplex analysis; col. 15, lines 60-63, where each individual probe is independently detectable).

With regard to claim 36, Hyldig-Nielsen teach an embodiment of claim 1, wherein said target is a bacterium or component or product thereof (Table 2, where PNA probes are directed to detect bacteria; Example 12, col. 28, lines 26-43, where a culture of *E. coli* is examined using the multiplex-PNA-FISH method disclosed).

With regard to claim 37, Hyldig-Nielsen teach an embodiment of claim 1, wherein said target is a yeast or component or product thereof (Table 2, where PNA probes are directed to detect eucarya; Example 12, col. 28, lines 44-65, where a culture of *Saccharomyces cerevisiae* is examined using the multiplex-PNA-FISH method disclosed).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the PNA probe and the plurality of probes taught by Hyldig-Nielsen into the method of hybridization and detection of nucleic acids. As noted by Hyldig-Nielsen, the inclusion of PNA probes specifically provides that "Because the PNA probe can efficiently and preferably, hybridize to nucleic acid under these conditions of low salt, the PNA probes can be designed to target rRNA which cannot be targeted by traditional nucleic acid probes". Hyldig-Nielsen goes on to note that "PNA probes of this invention typically generate stronger signals than can be achieved with nucleic acid probes of comparable nucleobase sequence" (col. 14, lines 30-45). Furthermore, Hyldig-Nielsen teaches that, "the ability to differentiate between and/or quantitate each of the independently detectable moieties provides the means to multiplex a hybridization assay because the data which correlates with the hybridization of each of the distinctly (independently) labeled probe to a particular target sequence can be correlated with the presence, absence or quantity of each organism sought to be detected in the sample. Consequently, the multiplex assays of this invention may be used to simultaneously detect the presence, absence or quantity of two or more organisms in the same sample and in the same assay" (col. 7, line 66 to col. 8 line 9). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the PNA probes as described by Hyldig-Nielsen into the method of nucleic acid detection taught by Lorincz in

order to achieve the stated benefit of increased signal strength and probes which target regions inaccessible to traditional nucleic acid probes with a reasonable expectation for success.

6. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Kumar et al. (Bioorganic & Medicinal Chemistry, 1998, vol. 8, p. 2219-2222). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a probe which comprises locked nucleic acid.

Kumar teaches the improvement of duplex stability provided by the inclusion of a locked nucleic acid probe into a method where recognition of complementary DNA or RNA was necessary (Abstract).

With regard to claim 6, Kumar teach an embodiment of claim 1, wherein the sensor comprises a locked nucleic acid (Abstract, p. 2219, where it is noted that LNA provides stability against 3'-exonucleolytic degradation, efficient automated synthesis, good solubility and improved stability of duplexes with DNA or RNA).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the LNA probe taught by Kumar into the method of nucleic acid detection taught by Lorincz. As noted by Kumar, the inclusion of LNA probes specifically

provides, "unprecedented thermal stabilities of duplexes towards complementary DNA and RNA" , stability towards 3'-exonucleolytic degradation, efficient automated oligomerization and good aqueous solubility (p. 2219). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the LNA probe taught by Kumar in order to achieve the stated benefit of improved thermal stability of duplexes formed with either DNA or RNA target molecules.

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Bruchez, Jr. et al. (Science, 1998, vol. 281, p. 2013-2016). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a semiconductor nanocrystal as the detectable label.

Bruchez, Jr. teaches the inclusion of a semiconductor nanocrystal into a method of biological staining and diagnostics (Abstract).

With regard to claim 10, Bruchez, Jr. teach an embodiment of claim 9, wherein the fluorophore is a semiconductor nanocrystal (Abstract, Figure 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the semiconductor nanocrystal taught by Bruchez, Jr. into the

method of nucleic acid detection taught by Lorincz. As noted by Bruchez, Jr, the semiconductor nanocrystal label provide the benefit that "many sizes of nanocrystals may therefore be excited with a single wavelength of light, resulting in many emission colors that may be detected simultaneously" (p. 2014, col. 1). Furthermore, Bruchez, Jr. teach that "the tenability of the optical features allows for their use as direct probes or as sensitizers for traditional probes. These nanocrystals also have a long fluorescence lifetime, which can allow for time-gated detection of autofluorescence suppression" (p. 2015, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the semiconductor nanocrystal taught by Bruchez, Jr. in order to achieve the stated benefit of a label that is excitable by a single wavelength of light yet able to provide multiple colors of emission, particularly for the detection of multiple targets simultaneously.

8. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Ylikoski et al. (US Patent 5,256,535; October 1993). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a lanthanide chelate as the detectable label.

Ylikoski teaches the inclusion of a lanthanide chelate into a method of hybridization (Abstract).

With regard to claim 13, Ylikoski teach an embodiment of claim 9, wherein the fluorophore is a lanthanide chelate (Abstract; col. 3, lines 44-52; col. 4, lines 17-21).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the lanthanide chelate label taught by Ylikoski into the method of nucleic acid detection taught by Lorincz. As noted by Ylikoski, the inclusion of a lanthanide chelate label specifically provide that "the intensity of fluorescence emitted from the double stranded nucleic acid is a quantitative measure of the nucleotide sequence to be determined" (col. 4, lines 25-28). Ylikoski goes on to note that "the important feature in the invention is the use of water soluble polymeric compounds as a matrix to which a large number of europium or terbium chelates are covalently coupled. This covalent coupling gives a large amplification of the detectable signal" (col. 4, lines 35-42). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the lanthanide chelate label taught by Ylikoski in order to achieve the stated benefit of increased signal strength with a reasonable expectation for success.

9. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Fukasawa et al. (Science, 1996, vol. 271, p. 1744-1747). Lorincz teaches a universal collection medium for

cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above.. However, Lorincz does not teach the examination of a centrosomal target.

Fukusawa teach an examination of centrosomes in cells where the p53 tumor suppressor gene is mutated (Abstract).

With regard to claim 17, Fukusawa teach an embodiment of claim 1, wherein the target is centrosomal (Abstract, Figures 1-2, where centrosomes were identified in mouse embryonic fibroblasts with wildtype and mutated p53 using an antibody to γ-tubulin).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the centrosomal target taught by Fukusawa into the method of nucleic acid detection taught by Lorincz. As noted by Fukusawa, the centrosomal target was crucial and in cells where p53 was mutated, "the presence of multiple centrosomes in the mitotic spindles had profound effects on chromosome segregation; the chromosomes did not partition during anaphase because they were captured by astral microtubules of one centrosome (or a few centrosomes) localized outside of the poles". Fukusawa goes on to note that "when large numbers of centrosomes failed to localize at the poles in a bipolar fashion, the proper spindle apparatus did not form" (p. 1746, col. 1-2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the centrosomal target taught by Fukusawa in order to determine the proper chromosomal segregation in a cellular target with a reasonable expectation for success.

(10) Response to Argument

First, regarding the rejection of claim 28 as being anticipated by Lorincz, Applicant traverses. Applicant looks to Example 1 of Challberg (WO96/10263) and note that the method requires removal of a 150 ul aliquot, added to 50 ul of diluent containing Probe A, B or C. Applicant concludes that the contacting of the target with a probe takes place in a different solution and not in the preservative solution. Applicant also asserts that the preservative solution must contain "...an amount of one or more water soluble alcohols effective to preserve such solution". Applicant also disagrees "that contacting a sample with a sensor in the presence of a preservative solution is the same as contacting a sample with a sensor in a preservative solution" (p. 6-8 of brief). Finally, Applicant notes that the Examples cited from Lorincz "require the manipulation of preserved cells outside of the original solution in which the cells are collected" and "the cells are no longer in the original collection solution and no further hybridizations, bindings or other experimental protocols takes place in that solution" (p. 8 of brief).

These arguments are not persuasive.

The main issue of this case comes down to different interpretations of the claimed invention. Claim 28 requires contact between a sample suspected of containing a target and a detectable sensor. The sample is contacted by the sensor in a preservative solution comprising an amount of one or more water-soluble alcohols effective to preserve the solution against a contaminant and that does not comprise formamide. The binding of the sensor to the target is then detected.

Based on the arguments summarized above, Applicant is interpreting the claim as narrowly requiring that the preservative solution in which the sample was collected is the same solution used throughout the method and particularly during the contact of the sample with the detectable sensor. In response, it is noted that there is no requirement in the claim that the sample is collected in the preservative solution. Next, it is noted that there is no requirement in the claim that the preservative solution is the same solution throughout the initial contacting step, or for the hybridization and detection steps. The method as claimed comprises these elements and steps and does not preclude pulling an aliquot of the sample out of the original solution for hybridization in another solution while maintaining the presence of the preservative solution in the aliquot.

Regarding the anticipation of the claim by Lorincz, the claim is being interpreted as simply requiring that the sensor is in contact with the target in a solution that does not contain formamide and that the solution comprises alcohol when the contacting occurs. Lorincz specifically teaches multiple preservative solutions comprising water-soluble alcohol and no formamide. Lorincz teaches a method that comprises detecting the nucleic acid in the sample, the sample (cells) are present in the UCM formulations comprising an amount of alcohol and the nucleic acid is detected using a method that comprises lysis and hybridization with a biotinylated probe, thus anticipated the method as claimed.

Specifically, In Example 1, Lorincz teaches a general assay for nucleic acids in the samples and that the method follows in principle the Digene Hybrid Capture HIV test described in WO93/10263. Lorincz describes the method as 'Briefly, following lysis, 50 ul of probe mix (containing DNA biotinylated probe) was added to each well'. The steps prior to lysis are

addressed in Example 1 of WO93/10263 as comprising collection of cervical specimens in a preservative solution, hydrolysis reagent is added and following this lysing step, an aliquot was removed and added to the probe mix containing the sensor.

In summary the method comprises analysis of cervical samples in solution, lysis buffer is added to the cells in the preservative solution. Following the contact between the cells and the lysis buffer, an aliquot is removed without an intermediate washing step. Therefore, the alcohol present in the original preservative solution is maintained in the aliquot and the hybridization reaction occurs in some 'amount of' alcohol, thereby meeting the limitation of the method as claimed.

Applicant traverses the rejection of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as being unpatentable over Lorincz in view of Shah. Applicant reiterates the arguments as stated above that Lorincz does not teach or suggest contacting a sample with a sensor in an alcoholic preservative solution that does not contain formamide under conditions in which the sensor can bind to the target. Regarding Shah, Applicant states that the deficiencies in Lorincz cannot be overcome by Shah. These arguments are not persuasive for the reasons stated above regarding the rejection of claim 28. The Shah reference is relied upon for the teaching of labeling with a fluorophore that would be detected using light emission and detection as recited in claim 1.

Applicant traverses the rejection of claims 20-22 as being unpatentable over Lorincz in view of Shah and further in view of Challberg. Applicant reiterates the arguments are stated above that the Examiner has not pointed with specificity to any teaching or suggestion in Lorincz

or Shah alone or in combination that recites all of the limitations of claim 1. Regarding Challberg, Applicant states that the deficiencies in Lorincz and Shah cannot be overcome by Challberg and states that there is no suggestion or teaching in Challberg of detecting nucleic acids in a preservative solution. These arguments are not persuasive for the reasons stated above regarding Lorincz and Shah. Regarding Challberg, Applicant is not correct that Challberg does not provide a teaching or suggestion of detecting nucleic acids in a preservative solution. As noted above in connection with the method taught by Lorincz, Challberg (WO93/10263) does teach detecting nucleic acids in preservative solution, ViraPap, at Example 1. Furthermore, at p. 13, Challberg specifically teaches that the cells are collected and "stored in a transport medium that preserves nucleic acids and inhibits nucleases" (p. 13, lines 8-24) and provides ViraPap as a example of a preservative transport medium. Therefore, the rejection is maintained.

Applicant traverses the rejection of claims 5, 7, 29 and 36-37 as being unpatentable over Lorincz, Shah and Hyldig-Nielsen. Applicant traverses the rejection of claim 6 as being unpatentable over Lorincz, Shah and Kumar. Applicant traverses the rejection of claim 10 as being unpatentable over Lorincz, Shah and Bruchez, Jr. Applicant traverses the rejection of claim 13 as being unpatentable over Lorincz, Shah and Ylikoski. Applicant also traverses the rejection of claim 17 as being unpatentable over Lorincz, Shah and Fukusawa.

For each of these rejections, Applicant's reiterated the argument that "the Examiner has not pointed with specificity to any teaching or suggestion in Lorincz with Shah either alone or in combination that recites all the limitations of claim 1". Applicant, in each case, notes that the deficiency in Lorincz and Shah cannot be overcome by the additional reference and that there is

no suggestion or teaching in the additional reference of detecting target nucleic acids in preservative solution. These arguments are not persuasive for the same reasons stated above regarding the Lorincz reference.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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